4-Nonanone, 2,6,8-Trimethyl-

(Isobutyl Heptyl Ketone; IBHK; CAS RN 123-18-2)

High Production Volume (HPV) Chemical Challenge Test Plan and Data Review

Prepared for:

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4-Nonanone, 2,6,8-Trimethyl- (Isobutyl Heptyl Ketone; CAS RN: 123-18-2		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	Testing Required
STUDY		**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**	**Y/N**
PHYSICAL AND CHEMICAL DATA								
2.1	Melting Point	Y	N	N	Y	N	Y	N
2.2	Boiling Point	Y	N	N	Y	N	Y	N
2.4	Vapor Pressure	Y	N	N	Y	N	Y	N
2.5	Partition Coefficient	Y	N	N	N	Y	Y	N
2.6	Water Solubility	Y	N	Y	Y	N	Y	N
ENVIRONMENTAL FATE AND PATHWAY								
3.1.1	Photodegradation	Y	N	N	N	Y	Y	N
3.1.2	Stability in Water	Y	N	N	Y	N	Y	N
3.3	Transport and Distribution	Y	N	N	N	Y	Y	N
3.5	Biodegradation	Y	Y	Y	N	N	Y	N
ECOTOXICITY								
4.1	Acute Toxicity to Fish	Y	Y	Y	N	N	Y	N
4.2	Toxicity to Daphnia	Y	Y	Y	N	N	Y	N
4.3	Acute Toxicity to Algae	Y	Y	Y	N	N	Y	N
TOXICITY								
5.1	Acute Toxicity	Y	N	N	Y	N	Y	N
5.4	Repeated Dose Toxicity	Y	Y	Y	N	N	N	N
5.5	Genotoxicity *In Vitro* (Bacterial Test)	Y	Y	Y	N	N	N	N
5.5	Genotoxicity *In Vitro* (Mammalian Cells)	Y	Y	Y	N	N	N	N
5.8.	Reproductive Toxicity	Y	Y	Y	N	N	N	N
5.9	Development Toxicity / Teratogenicity	Y	Y	Y	N	N	N	N

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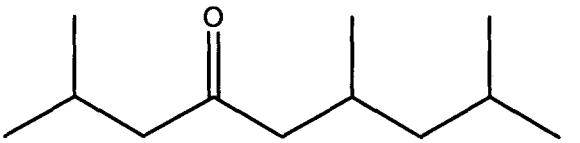
1.0 Introduction

This document provides the Final Test Plan Status and reviews the data availability for the High Production Volume (HPV) Chemical Challenge endpoints for 4-Nonanone, 2,6,8-trimethyl-, hereafter called Isobutyl Heptyl ketone [IBHK; CAS RN 123-18-2]. IBHK is sponsored by The Dow Chemical Company.

2.0 General Use and Exposure

Isobutyl Heptyl Ketone is a high molecular weight ketone produced exclusively by The Dow Chemical Company and marketed under the trade name ECOSOFT™ Solvent IK. It is used as an intermediate to make an extraction solvent for mining and in the production of 2,6,8-trimethyl-4-nonanol. During 2002, between 1 and 3 million pounds were produced either for sale to the mining industry or to be hydrogenated into an alcohol for internal use. Because of its excellent solvent properties, isobutyl heptyl ketone can be used in industrial cleaners and degreasers, and with the trend toward low volatility solvents with strong solvency, it may find additional uses in coating applications.

3.0 General Substance Information (Identity)

Chemical Name	4-Nonanone, 2,6,8-Trimethyl-
Synonyms	Isobutyl Heptyl Ketone (IBHK) 2,6,8-Trimethyl-4-nonanone 2,6,8-Trimethylnonan-4-one
CAS Number	123-18-2
Structure	
Molecular Weight	184.32
Substance Type	Organic
Physical State	Liquid
Odor	Obnoxious
Purity	2,6,8-Trimethyl-4-nonanone (CAS 123-18-2) >=95%; <=100% 4-Nonanol, 2,6,8-trimethyl- (CAS 123-17-1) <= 4%

4.0 Physical/Chemical Properties

A data summary for IBHK is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

4.1 Melting Point

The melting point for IBHK is listed as –75.2 °C (DIPPR, 2000). This value is considered adequate to meet the HPV Chemical Challenge requirements.

4.2 Boiling Point

The boiling point for IBHK is listed as 218.3 °C (DIPPR, 2000). This value is considered adequate to meet the HPV Chemical Challenge requirements.

4.3 Vapor Pressure

The vapor pressure for IBHK is listed as 0.074 hPa at 20 °C (DIPPR, 2000). This value is considered adequate to meet the HPV Chemical Challenge requirements.

4.4 Partition Coefficient

The log K_{ow} for IBHK is predicted by EPIWIN to be 3.96 (U.S. EPA, 2000a). This value is consistent with the known properties of IBHK and is considered adequate to meet the HPV Chemical Challenge requirements.

4.5 Water Solubility

The water solubility value for IBHK was determined using an ASTM method to be 22 mg/L (Wilson, 2000). Therefore, IBHK is only slightly soluble in water. This value is considered adequate to meet the HPV Chemical Challenge requirements.

5.0 Environmental Fate

A data summary for IBHK is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

5.1 Photodegradation

The model prediction for atmospheric photodegradation provides a second order rate of reaction with hydroxyl radicals of 23.2 E-12 cm^3/molecule-sec and a $t_{1/2}$ of 11 hours (12-hr day; 1.5E6 OH/cm^3) (U.S. EPA, 2003). The vapor pressure of IBHK (0.074 hPa) is low and significant quantities would not be expected in the atmosphere. Degradation of any accidental release would be anticipated based on the model prediction. These data are considered adequate to meet the HPV Chemical Challenge requirements.

5.2 Stability in Water

IBHK does not react with water; the only functionality other than carbon-carbon and carbon-hydrogen bonds is the carbonyl group which does not hydrolyze.

5.3 Transport and Distribution

The Level III fugacity model (U.S. EPA, 2003) was used to predict the distribution of IBHK released into the environment. Environmental exposure to IBHK is limited based on the use patterns as an industrial intermediate and solvent. For example, IBHK is not listed on the Toxic Release Inventory. Therefore, only accidental releases were considered for the fugacity modeling. Two scenarios, 100% release to air and 100% release to water were examined. For the air release the model predicted a distribution of 96% into atmosphere, 3% into water, 1% into soil, and < 1% into sediment. For the water release, the model predicted a distribution of 2% into atmosphere, 92% into water, < 0.1% into soil, and 6% into sediment. These data are considered adequate to meet the HPV Chemical Challenge requirements.

5.4 Biodegradability

A biodegradation study with IBHK according to OECD Guideline 301D indicated 44.7% degradation after 28 days. According to OECD Guideline, IBHK is not readily biodegradable (Davis and Marty, 2004).

6.0 Ecotoxicity

A data summary for IBHK is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

6.1 Toxicity to Fish

Acute toxicity study to rainbow trout (*Oncorhynchus mykiss)* according to OECD Guideline 203 yielded a 96-hour LC_{50} value > 1.24 mg/L. In this study, fish were exposed to nominal concentrations of IBHK of 0, 6.25, 12.5, 25.0, 50.0 and 100 mg/L. However, analytical verification resulted in the highest exposure concentration being 1.24 mg/L due to the limited solubility. No mortality occurred in this study. Therefore, the LC_{50} value was > 1.24 mg/L and the NOEC was 1.24 mg/L (Marino et al., 2003a).

6.2 Toxicity to Aquatic Invertebrates

An acute toxicity study with *Daphnia magna* according to OECD Guideline 202 yielded a 48-hour EC_{50} value of 3.41 mg/L. Nominal exposure concentrations were 1.56, 3.13, 6.25, 12.5, 25.0, 50.0 and 100 mg/L. After 48 hours, immobility was observed in 100%, 95%, 65% and 25% of the daphnia at analytical concentrations of 11.6, 9.19, 4.51, and 2.12 mg/L, respectively. The EC_{50} value was determined based on the analytical values. (Marino et al., 2003b).

6.3 Toxicity to Aquatic Plants

A toxicity study with the green alga, *Pseudokirchneriella subcapitata,,* according to OECD Guideline 201 yielded a 96-hour EC_{50} value > 1.3 mg/L. Nominal exposure concentrations were 3.13, 6.25, 12.5, 25.0, 50.0 and 100 mg/L.. However, analytical verification resulted in the highest exposure concentration being 1.3 mg/L due to the limited solubility. No effects on algal growth occurred in this study. Therefore, the EC_{50} value was > 1.3 mg/L and the NOEC was 1.3mg/L (Hancock et al., 2003).

7.0 Human Health-Related Data

A data summary for IBHK is included in Table 1. The Robust Summaries are included in the IUCLID Dataset.

7.1 Acute Toxicity

The following acute toxicity data are available: acute oral LD_{50} in rats = 8470 mg/kg bw; acute dermal LD_{50} in rabbits = 9030 mg/kg bw; 2 of 6 rats died after an 8-hr exposure to substantially saturated vapor; and 6 of 6 rats died when exposed to the test substance as a cooled mist for one hour (Carpenter, 1948). These data are considered adequate to meet the HPV Chemical Challenge requirements.

7.2 Repeated Dose Toxicity

Male and female CD rats were dosed with IBHK at 0, 100, 300, or 1000 mg/kg/day in a study conducted according to OECD Guideline 422. Treatment-related effects in males included increased salivation and perioral soiling (all doses), perineal soiling (1000 mg/kg/day), increases in serum cholesterol, AST and total protein and in prothrombin time (1000 mg/kg/day), increased urine pH (1000 mg/kg/day), increased liver weight (100, 300, and 1000 mg/kg/day), increased kidney weight (100 and 300 mg/kg/day), and increased thyroid weight (1000 mg/kg/day). Histopathologically, male rats exhibited degenerative effects of the kidneys and hyaline droplet formation in the renal proximal tubules (all doses), panlobular hepatocellular hypertrophy (all doses), and follicular epithelial cell hypertrophy of the thyroid gland (all doses). Treatment related effects in females included increased salivation (all doses) and perineal soiling (1000 mg/kg/day), increased serum cholesterol and ALP (1000 mg/kg/day), increased liver weight (all doses), increased relative kidney weight (300 and 1000 mg/kg/day), increased thyroid weight (300 and 1000 mg/kg/day), and increased incidence of centrilobular hepatocellular hypertrophy (300 and 1000 mg/kg/day). No other treatment-related effects were observed including on parameters used to assess neurotoxicity. The NOAEL for males could not be determined from this study; the NOAEL for females was 100 mg/kg/day. The NOAEL for neurological effects was 1000 mg/kg/day (Carney et al., 2005).

7.3 Genetic Toxicity (*in vitro*)

IBHK was tested in the bacterial reverse mutation assay test (OECD Guideline 471) with *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537 and *Escherichia coli*, WP2*uvr*A at concentrations up to 5000 μg/plate with and without metabolic activation. IBHK was considered not mutagenic under the conditions of the assay (Charles et al., 2004).

IBHK was tested in a cytogenetic assay (rat lymphocytes) according to OECD Guideline 473 at concentrations up to 60 μg/ml without metabolic activation and up to 120 μg/ml with metabolic activation. IBHK was negative with and without metabolic activation in this assay (Linscombe et al., 2004).

7.4 Reproductive and Developmental Toxicity

Male and female CD rats were dosed with IBHK at 0, 100, 300, or 1000 mg/kg/day in a study conducted according to OECD Guideline 422. There were no treatment-related effects at any dose level on any of the reproductive parameters, pup survival indices or sex ratio. Decreases in pup body weights of male and female pups were observed on pnd day 1 and 4 in the 1000 mg/kg/day dose group. The NOEL for reproductive effects was 300 mg/kg/day (Carney et al., 2005).

In a dose ranging finding probe study based on EPA OPPTS 370.3700 guideline, female rats were dosed with IBHK at 0, 250, 500, 750 or 1000 mg/kg/day on gestation days 6-20. Treatment-related effects on the dams included decreased body weight gain (750 and 1000 mg/kg/day), increased liver weights (500, 750 and 1000 mg/kg/day) and increased kidney weights (1000 mg/kg/day). Mean percent postimplantation loss was increased to 9.27% (compared to the control value of 3.13%). No other treatment-related effects were observed (Marty et al., 2002).

8.0 Conclusion

Adequate information is available for melting point, boiling point, vapor pressure and water solubility of IBHK. Partition coefficient, photodegradation and environmental distributions are adequately supported by the appropriate model data. IBHK does not have hydrolyzable groups and is stable in abiotic aqueous systems. IBHK is not readily biodegradable but is ultimately degraded (~45% over 28 days).

IBHK is toxic to aquatic invertebrates with an EC50 of 3.41 mg/L. Due to the low solubility of IBHK, toxicity to fish and aquatic plants could not be definitively established (no toxicity observed at the highest soluble concentration of approximately 1.3 mg/L).

In mammals, IBHK is relatively non-toxic following acute oral and dermal exposure. Inhalation exposure may result in toxicity to the lung, although significant exposure is not anticipated based on the low vapor pressure and the obnoxious odor of IBHK. Male rats were more susceptible to IBHK toxicity after 4 – 8 weeks (OECD 422) of dosing, exhibiting liver hypertrophy at lower doses than females and thyroid hypertrophy at all doses tested (100, 300 and 1000 mg/kg/day) that was not observed in females. Male rat kidneys were also affected (degeneration) at doses $\geq$ 300 mg/kg/day; however, the potential existed for the kidney effects to be mediated through the male rat-specific, alpha-2u-globulin hyaline droplet nephropathy. In the OECD 422 study, IBHK did not affect reproduction at any dose tested although neonatal body weights were reduced at the highest, maternally toxic dose. In a developmental toxicity probe study, the percentage of post-implantation losses was higher in the high dose group (1000 mg/kg/day) but , as noted, no reproductive effects were noted in the OECD 422 study design. The NOAEL for adult toxicity was not identified for male rats in the available studies based on effects on liver and thyroid (and potentially kidney); the NOAEL was 100 mg/kg/day for adult females. The NOAEL for neonates was 300 mg/kg/day.

9.0 References

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Table 1: HPV Data Summary

4-Nonanone, 2,6,8-Trimethyl-
(Isobutyl Heptyl Ketone; IBHK)

CAS NO: 123-18-2		SPECIES	PROTOCOL	RESULTS
PHYSICAL-CHEMICAL				
2.1	Melting Point		Handbook Data (DIPPR)	-75.2 ºC
2.2	Boiling Point		Handbook Data (DIPPR)	218.3 ºC
2.3	Density		Handbook Data (DIPPR)	0.818 g/cm^3 (at 20 ºC)
2.4	Vapor Pressure		Handbook Data (DIPPR)	0.07413 hPa (at 20 ºC)
2.5	Partition Coefficient (log K_{ow})		KOWWIN v 1.67	3.96
2.6	Water Solubility		ASTM E 1148	22 mg/L
2.7	Flash Point		Handbook Data (DIPPR)	82.9 ºC
ENVIRONMENTAL FATE AND PATHWAY				
3.1.1	Photodegradation		AOPWIN v 1.91	half-life: 11 hours (12 hour day; OH Rate Constant)
3.1.2	Stability in Water		Hydrolysis @ 25 °C	Does not react with water; the only functionality other than carbon-carbon and carbon-hydrogen bonds is the carbonyl group which does not hydrolyze
3.3	Transport and Distribution		Mackay Level III 100% release to air	96% into atmosphere, 3% into water, 1% into soil, < 1% into sediment
			Mackay Level III 100% release to water	2% into atmosphere, 92% into water, < 0.1% into soil, 6% into sediment
3.5	Biodegradation		OECD 301D	44.7% degraded in 28 days
ECOTOXICOLOGY				
4.1	Acute/Prolonged Toxicity to Fish	*Oncorhynchus mykiss*	OECD 203	LC_{50} > 1.24 mg/L (highest soluble concentration)
4.2	Acute Toxicity to Aquatic Invertebrates	*Daphnia magna*	OECD 202	LC_{50} = 3.41 mg/L
4.3	Toxicity to Aquatic Plants e.g. Algae	*Pseudokirchneriella subcapitata*	OECD 201	LC_{50} > 1.3 mg/L (highest soluble concentration)

Table 1: HPV Data Summary

4-Nonanone, 2,6,8-Trimethyl-
(Isobutyl Heptyl Ketone; IBHK)

CAS NO: 123-18-2		SPECIES	PROTOCOL	RESULTS
TOXICOLOGY				
5.1.1	Acute Oral Toxicity	Rat	Not specified	LD_{50}: 8470 mg/kg bw
5.1.2	Acute Inhalation Toxicity	Rat	Saturated vapor	2/6 dead @ 8 hr.
		Rat	Cooled mist	6/6 dead @ 1 hr
5.1.3	Acute Dermal Toxicity	Rabbit	Not specified	LD_{50}: 9030 mg/kg bw
5.4	Repeated Dose Toxicity	Rat	OECD 422	NOAEL Females = 100 mg/kg/day NOAEL Males < 100 mg/kg/day
5.5	Genetic Toxicity *In Vitro*			
	Bacterial Test (Gene mutation)	*Salmonella typhimurium*	OECD 471	Negative (with and without metabolic activation)
	Chromosomal aberration	Rat lymphocytes	OECD 473	Negative (with and without metabolic activation)
5.8	Toxicity to Reproduction / Impairment of Fertility	Rat	OECD 422	No effects on reproductive parameters; neonatal weight decreased at 1000 mg/kg/day; NOAEL = 300 mg/kg/day
5.9	Developmental Toxicity / Teratogenicity	Rat	OECD 422	No developmental toxicity up to 1000 mg/kg/day